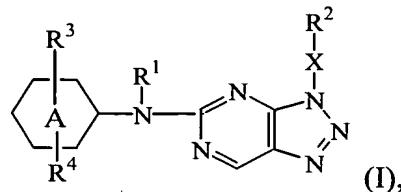


Claims

1. A compound of formula



a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine and a
5 stereochemically isomeric form thereof, wherein

ring A represents phenyl, pyridyl, pyrimidinyl, pyridazinyl or pyrazinyl;

R¹ represents hydrogen; aryl; formyl; C₁₋₆alkylcarbonyl; C₁₋₆alkyl;

C₁₋₆alkyloxycarbonyl; C₁₋₆alkyl substituted with formyl, C₁₋₆alkylcarbonyl,

C₁₋₆alkyloxycarbonyl, C₁₋₆alkylcarbonyloxy; or C₁₋₆alkyloxyC₁₋₆alkylcarbonyl

10 optionally substituted with C₁₋₆alkyloxycarbonyl;

X represents a direct bond; -(CH₂)_{n3}- or -(CH₂)_{n4}-X_{1a}-X_{1b}-;

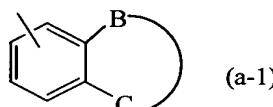
with n₃ representing an integer with value 1, 2, 3 or 4;

with n₄ representing an integer with value 1 or 2;

with X_{1a} representing O, C(=O) or NR⁵; and

15 with X_{1b} representing a direct bond or C₁₋₂alkyl;

R² represents C₃₋₇cycloalkyl; phenyl; a 4, 5, 6- or 7-membered monocyclic heterocycle
containing at least one heteroatom selected from O, S or N; benzoxazolyl or a
radical of formula



20 wherein -B-C- represents a bivalent radical of formula

-CH₂-CH₂-CH₂- (b-1);

-CH₂-CH₂-CH₂-CH₂- (b-2);

-X₁-CH₂-CH₂-(CH₂)_n- (b-3);

-X₁-CH₂-(CH₂)_n-X₁- (b-4);

-X₁-(CH₂)_n-CH=CH- (b-5);

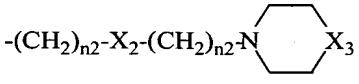
-CH=N-X₁- (b-6);

with X₁ representing O or NR⁵;

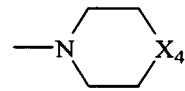
n representing an integer with value 0, 1, 2 or 3;

n' representing an integer with value 0 or 1;

25 30 wherein said R² substituent, where possible, may optionally be substituted with at
least one substituent selected from halo; hydroxy; C₁₋₆alkyl optionally substituted
with at least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy,

C₁₋₄alkyloxyC₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR⁶R⁷, -C(=O)-NR⁶R⁷, -NR⁵-C(=O)-NR⁶R⁷, -S(=O)_{n1}-R⁸ or -NR⁵-S(=O)_{n1}-R⁸; C₂₋₆alkenyl or C₂₋₆alkynyl, each optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, 5 C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR⁶R⁷, -C(=O)-NR⁶R⁷, -NR⁵-C(=O)-NR⁶R⁷, -S(=O)_{n1}-R⁸ or -NR⁵-S(=O)_{n1}-R⁸; polyhalo-C₁₋₆alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkyloxyC₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR⁶R⁷, -C(=O)-NR⁶R⁷, 10 -NR⁵-C(=O)-NR⁶R⁷, -S(=O)_{n1}-R⁸ or -NR⁵-S(=O)_{n1}-R⁸; C₁₋₆alkyloxy optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyl-oxycarbonyl, C₁₋₄alkylcarbonyloxy, NR⁶R⁷, -C(=O)-NR⁶R⁷, -NR⁵-C(=O)-NR⁶R⁷, -S(=O)_{n1}-R⁸ or -NR⁵-S(=O)_{n1}-R⁸; polyhaloC₁₋₆alkyloxy optionally substituted with at least one substituent selected 15 from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkyloxyC₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR⁶R⁷, -C(=O)-NR⁶R⁷, -NR⁵-C(=O)-NR⁶R⁷, -S(=O)_{n1}-R⁸ or -NR⁵-S(=O)_{n1}-R⁸; C₁₋₆alkylthio; polyhaloC₁₋₆alkylthio; C₁₋₆alkyloxycarbonyl; C₁₋₆alkylcarbonyloxy; C₁₋₆alkylcarbonyl; polyhaloC₁₋₆alkylcarbonyl; cyano; carboxyl; NR⁶R⁷; 20 C(=O)NR⁶R⁷; -NR⁵-C(=O)-NR⁶R⁷; -NR⁵-C(=O)-R⁵; -S(=O)_{n1}-R⁸; -NR⁵-S(=O)_{n1}-R⁸; -S-CN; -NR⁵-CN; aryloxy; arylthio; arylcarbonyl; arylC₁₋₄alkyl; arylC₁₋₄alkyloxy; a 5-or 6-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N and said 5-or 6-membered monocyclic heterocycle optionally being substituted with at least one substituent selected from R⁹; or 25 -(CH₂)_{n2}-X₂-(CH₂)_{n2}N; with n2 representing an integer with value 0, 1, 2, 3 or 4; with X₂ representing O, NR⁵ or a direct bond; with X₃ representing O, CH₂, CHO₂, CH-N(R⁵)₂, NR⁵ or N-C(=O)-C₁₋₄alkyl; 30 R³ represents halo; hydroxy; C₁₋₆alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkyloxyC₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR^{6b}R^{7b}, -C(=O)-NR^{6b}R^{7b}, -NR⁵-C(=O)-NR^{6b}R^{7b}, -S(=O)_{n1}-R^{8a} or -NR⁵-S(=O)_{n1}-R^{8a}; C₂₋₆alkenyl or C₂₋₆alkynyl, each optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, 35 C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR^{6b}R^{7b},

-C(=O)-NR^{6b}R^{7b}, -NR⁵-C(=O)-NR^{6b}R^{7b}, -S(=O)_{n1}-R^{8a} or -NR⁵-S(=O)_{n1}-R^{8a};
polyhaloC₁₋₆alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy,
C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR^{6b}R^{7b},
5 -C(=O)-NR^{6b}R^{7b}, -NR⁵-C(=O)-NR^{6b}R^{7b}, -S(=O)_{n1}-R^{8a} or -NR⁵-S(=O)_{n1}-R^{8a};
C₁₋₆alkyloxy optionally substituted with one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxy-carbonyl,
C₁₋₄alkylcarbonyloxy, NR^{6b}R^{7b}, -C(=O)-NR^{6b}R^{7b}, -NR⁵-C(=O)-NR^{6b}R^{7b},
-S(=O)_{n1}-R^{8a} or -NR⁵-S(=O)_{n1}-R^{8a}; polyhaloC₁₋₆alkyloxy optionally substituted with
10 at least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy,
C₁₋₄alkyloxyC₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl,
C₁₋₄alkylcarbonyloxy, NR^{6b}R^{7b}, -C(=O)-NR^{6b}R^{7b}, -NR⁵-C(=O)-NR^{6b}R^{7b},
-S(=O)_{n1}-R^{8a} or -NR⁵-S(=O)_{n1}-R^{8a}; C₁₋₆alkylthio; polyhaloC₁₋₆alkylthio;
C₁₋₆alkyloxycarbonyl; C₁₋₆alkylcarbonyloxy; C₁₋₆alkylcarbonyl; polyhalo-
15 C₁₋₆alkylcarbonyl; cyano; carboxyl; aryloxy; arylthio; arylcarbonyl; NR^{6b}R^{7b},
C(=O)-NR^{6b}R^{7b}, -NR⁵-C(=O)-NR^{6b}R^{7b}; -NR⁵-C(=O)-R⁵; -S(=O)_{n1}-R^{8a};
-NR⁵-S(=O)_{n1}-R^{8a}; -S-CN; or -NR⁵-CN;
R⁴ represents hydrogen; halo; hydroxy; C₁₋₄alkyl optionally substituted with at least one
20 substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl,
C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR¹⁰R¹¹, -C(=O)-NR¹⁰R¹¹,
-NR⁵-C(=O)-NR¹⁰R¹¹, -S(=O)_{n1}-R¹² or -NR⁵-S(=O)_{n1}-R¹²; C₂₋₄alkenyl or
C₂₋₄alkynyl, each optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl,
C₁₋₄alkylcarbonyloxy, NR¹⁰R¹¹, -C(=O)-NR¹⁰R¹¹, -NR⁵-C(=O)-NR¹⁰R¹¹,
25 -S(=O)_{n1}-R¹² or -NR⁵-S(=O)_{n1}-R¹²; polyhaloC₁₋₃alkyl; C₁₋₄alkyloxy optionally
substituted with carboxyl; polyhaloC₁₋₃alkyloxy; C₁₋₄alkylthio;
polyhaloC₁₋₃alkylthio; C₁₋₄alkyloxycarbonyl; C₁₋₄alkylcarbonyloxy;
C₁₋₄alkylcarbonyl; polyhaloC₁₋₄alkylcarbonyl; nitro; cyano; carboxyl; NR¹⁰R¹¹;
C(=O)NR¹⁰R¹¹; -NR⁵-C(=O)-NR¹⁰R¹¹; -NR⁵-C(=O)-R⁵; -S(=O)_{n1}-R¹²;
30 -NR⁵-S(=O)_{n1}-R¹²; -S-CN; or -NR⁵-CN;
R⁵ represents hydrogen; C₁₋₄alkyl or C₂₋₄alkenyl;
R⁶ and R⁷ each independently represent hydrogen; cyano; C₁₋₆alkylcarbonyl optionally
substituted with C₁₋₄alkyloxy or carboxyl; C₁₋₆alkyloxycarbonyl;
C₃₋₇cycloalkylcarbonyl; adamantanylcarbonyl; C₁₋₄alkyloxyC₁₋₄alkyl; C₁₋₄alkyl
35 substituted with C₁₋₄alkyl-NR⁵-; C₁₋₆alkyl optionally substituted with at least one
substituent selected from halo, hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, polyhalo-



C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyloxy, $NR^{6a}R^{7a}$, $C(=O)NR^{6a}R^{7a}$ or R^{6a} and R^{7a} each independently represent hydrogen; C_{1-4} alkyl; C_{1-4} alkylcarbonyl or a 5- or 6-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N;

R^{6b} and R^{7b} each independently represent hydrogen; cyano; C_{1-6} alkylcarbonyl optionally substituted with C_{1-4} alkyloxy or carboxyl; C_{1-6} alkyloxycarbonyl; C_{3-7} cycloalkylcarbonyl; adamantanylcarbonyl; C_{1-4} alkyloxy C_{1-4} alkyl; C_{1-4} alkyl substituted with C_{1-4} alkyl- NR^5 ; C_{1-6} alkyl optionally substituted with at least one substituent selected from halo, hydroxy, cyano, carboxyl, C_{1-4} alkyloxy, polyhalo C_{1-4} alkyl, C_{1-4} alkyloxy- C_{1-4} alkyloxy, $NR^{6c}R^{7c}$ or $C(=O)NR^{6c}R^{7c}$;

R^{6c} and R^{7c} each independently represent hydrogen; C_{1-4} alkyl or C_{1-4} alkylcarbonyl; R^8 represents C_{1-4} alkyl optionally substituted with hydroxy; polyhalo C_{1-4} alkyl or NR^6R^7 ;

R^{8a} represents C_{1-4} alkyl optionally substituted with hydroxy; polyhalo C_{1-4} alkyl or $NR^{6b}R^{7b}$;

R^9 represents halo; hydroxy; C_{1-6} alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C_{1-4} alkyloxy, C_{1-4} alkylcarbonyl, C_{1-4} alkyloxycarbonyl, C_{1-4} alkylcarbonyloxy, NR^6R^7 , $-C(=O)-NR^6R^7$, $-NR^5-C(=O)-NR^6R^7$, $-S(=O)_{n1}-R^8$ or $-NR^5-S(=O)_{n1}-R^8$; C_{2-6} alkenyl or C_{2-6} alkynyl, each optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C_{1-4} alkyloxy, C_{1-4} alkylcarbonyl, C_{1-4} alkyloxycarbonyl, C_{1-4} alkylcarbonyloxy, NR^6R^7 , $-C(=O)-NR^6R^7$, $-NR^5-C(=O)-NR^6R^7$, $-S(=O)_{n1}-R^8$ or $-NR^5-S(=O)_{n1}-R^8$; polyhalo C_{1-6} alkyl; C_{1-6} alkyloxy optionally substituted with carboxyl; polyhalo C_{1-6} alkyloxy; C_{1-6} alkylthio; polyhalo C_{1-6} alkylthio; C_{1-6} alkyloxycarbonyl; C_{1-6} alkylcarbonyloxy; C_{1-6} alkylcarbonyl; cyano; carboxyl; NR^6R^7 ; $C(=O)NR^6R^7$; $-NR^5-C(=O)-NR^6R^7$; $-NR^5-C(=O)-R^5$; $-S(=O)_{n1}-R^8$; $-NR^5-S(=O)_{n1}-R^8$; $-S-CN$; or $-NR^5-CN$;

R^{10} and R^{11} each independently represent hydrogen; C_{1-6} alkyl; cyano; C_{1-6} alkylcarbonyl; C_{1-4} alkyloxy C_{1-4} alkyl; or C_{1-4} alkyl substituted with C_{1-4} alkyl- NR^5 ;

R^{12} represents C_{1-4} alkyl or $NR^{10}R^{11}$;

$n1$ represents an integer with value 1 or 2;

aryl represents phenyl or phenyl substituted with at least one substituent selected from halo, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} alkyloxy, cyano, nitro, polyhalo C_{1-6} alkyl or polyhalo C_{1-6} alkyloxy.

2. A compound according to claim 1 wherein

X represents a direct bond; $-(CH_2)_{n_3}-$ or $-(CH_2)_{n_4}-X_a-X_b-$;

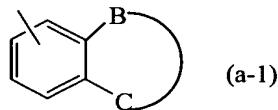
with n_3 representing an integer with value 1, 2, 3 or 4;

5 with n_4 representing an integer with value 1 or 2;

with X_a representing O or NR^5 ; and

with X_b representing a direct bond or C_{1-2} alkyl;

10 R^2 represents C_{3-7} cycloalkyl; phenyl or a 4, 5, 6- or 7-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N; or a radical of formula



(a-1)

wherein $-B-C-$ represents a bivalent radical of formula

$-CH_2-CH_2-CH_2-$ (b-1);

$-CH_2-CH_2-CH_2-CH_2-$ (b-2);

15 $-X_1-CH_2-CH_2-(CH_2)_{n_1}-$ (b-3);

$-X_1-CH_2-(CH_2)_n-X_1-$ (b-4);

$-X_1-(CH_2)_{n_1}-CH=CH-$ (b-5);

with X_1 representing O or NR^5 ;

20 n representing an integer with value 0, 1, 2 or 3;

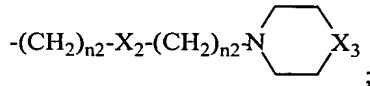
n' representing an integer with value 0 or 1;

wherein said R^2 substituent, where possible, may optionally be substituted with at least one substituent selected from halo; hydroxy; C_{1-6} alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C_{1-4} alkyloxy, C_{1-4} alkylcarbonyl, C_{1-4} alkyloxycarbonyl, C_{1-4} alkylcarbonyloxy, NR^6R^7 ,

25 $-C(=O)-NR^6R^7$, $-NR^5-C(=O)-NR^6R^7$, $-S(=O)_{n_1}-R^8$ or $-NR^5-S(=O)_{n_1}-R^8$; C_{2-6} alkenyl or C_{2-6} alkynyl, each optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C_{1-4} alkyloxy, C_{1-4} alkylcarbonyl, C_{1-4} alkyloxycarbonyl, C_{1-4} alkylcarbonyloxy, NR^6R^7 , $-C(=O)-NR^6R^7$, $-NR^5-C(=O)-NR^6R^7$, $-S(=O)_{n_1}-R^8$ or $-NR^5-S(=O)_{n_1}-R^8$; polyhalo C_{1-6} alkyl; C_{1-6} alkyloxy optionally substituted with

30 carboxyl; polyhalo C_{1-6} alkyloxy; C_{1-6} alkylthio; polyhalo C_{1-6} alkylthio; C_{1-6} alkyloxycarbonyl; C_{1-6} alkylcarbonyloxy; C_{1-6} alkylcarbonyl; polyhalo C_{1-6} alkylcarbonyl; cyano; carboxyl; NR^6R^7 ; $C(=O)NR^6R^7$; $-NR^5-C(=O)-NR^6R^7$; $-NR^5-C(=O)-R^5$; $-S(=O)_{n_1}-R^8$; $-NR^5-S(=O)_{n_1}-R^8$; $-S-CN$; $-NR^5-CN$; aryloxy; arylthio; arylcarbonyl; aryl C_{1-4} alkyl; aryl C_{1-4} alkyloxy; a 35 5-or 6-membered monocyclic heterocycle containing at least one heteroatom

selected from O, S or N and said 5-or 6-membered monocyclic heterocycle optionally being substituted with at least one substituent selected from R⁹; or



with n2 representing an integer with value 0, 1, 2, 3 or 4;

5 with X₂ representing O, NR⁵ or a direct bond;

with X₃ representing O or NR⁵;

R³ represents halo; hydroxy; C₁₋₆alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR^{6b}R^{7b}, -C(=O)-NR^{6b}R^{7b},

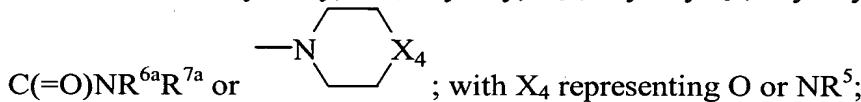
10 -NR⁵-C(=O)-NR^{6b}R^{7b}, -S(=O)_{n1}-R^{8a} or -NR⁵-S(=O)_{n1}-R^{8a}; C₂₋₆alkenyl or C₂₋₆alkynyl, each optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR^{6b}R^{7b}, -C(=O)-NR^{6b}R^{7b}, -NR⁵-C(=O)-NR^{6b}R^{7b}, -S(=O)_{n1}-R^{8a} or -NR⁵-S(=O)_{n1}-R^{8a}; polyhaloC₁₋₆alkyl; C₁₋₆alkyloxy optionally

15 substituted with carboxyl; polyhaloC₁₋₆alkyloxy; C₁₋₆alkylthio; polyhaloC₁₋₆alkylthio; C₁₋₆alkyloxycarbonyl; C₁₋₆alkylcarbonyloxy; C₁₋₆alkylcarbonyl; polyhaloC₁₋₆alkylcarbonyl; nitro; cyano; carboxyl; NR^{6b}R^{7b}; C(=O)NR^{6b}R^{7b}; -NR⁵-C(=O)-NR^{6b}R^{7b}; -NR⁵-C(=O)-R⁵; -S(=O)_{n1}-R^{8a}; -NR⁵-S(=O)_{n1}-R^{8a}; -S-CN; or -NR⁵-CN;

20 R⁵ represents hydrogen or C₁₋₄alkyl;

R⁶ and R⁷ each independently represent hydrogen; cyano; C₁₋₆alkylcarbonyl;

C₁₋₄alkyloxyC₁₋₄alkyl; C₁₋₄alkyl substituted with C₁₋₄alkyl-NR⁵; C₁₋₆alkyl optionally substituted with hydroxy, C₁₋₄alkyloxy, C₁₋₄alkyloxyC₁₋₄alkyloxy, NR^{6a}R^{7a},



25 R^{6a} and R^{7a} each independently represent hydrogen; C₁₋₄alkyl; C₁₋₄alkylcarbonyl or a 5- or 6-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N;

R^{6b} and R^{7b} each independently represent hydrogen; cyano; C₁₋₆alkylcarbonyl; C₁₋₄alkyloxyC₁₋₄alkyl; C₁₋₄alkyl substituted with C₁₋₄alkyl-NR⁵; C₁₋₆alkyl optionally

30 substituted with hydroxy, C₁₋₄alkyloxy, C₁₋₄alkyloxyC₁₋₄alkyloxy, NR^{6a}R^{7a} or C(=O)NR^{6a}R^{7a};

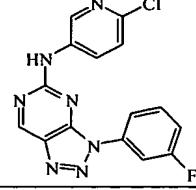
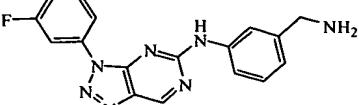
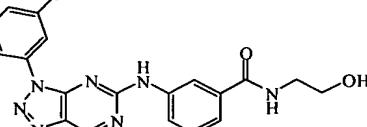
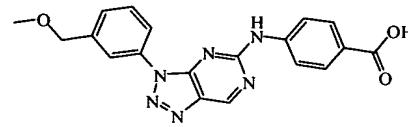
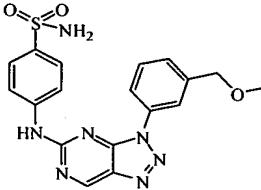
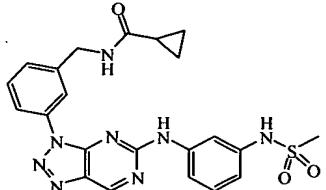
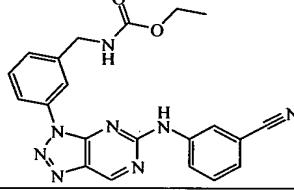
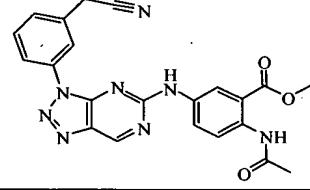
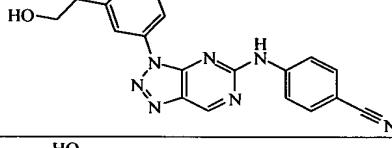
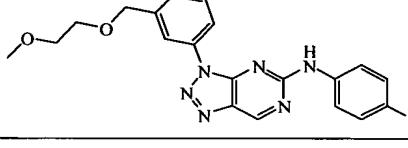
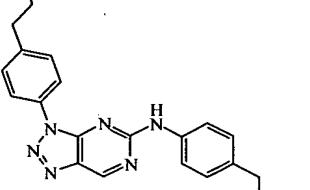
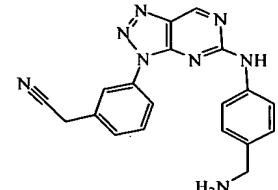
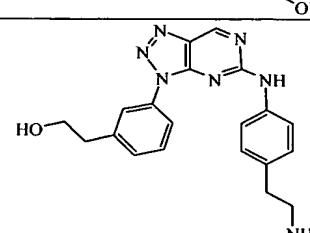
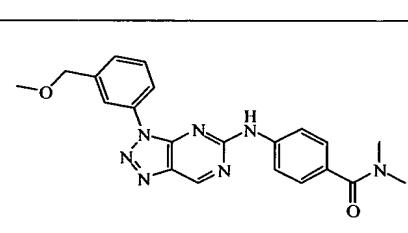
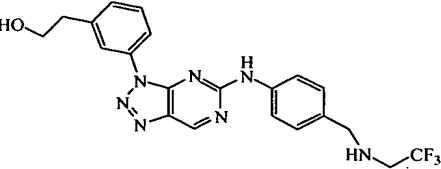
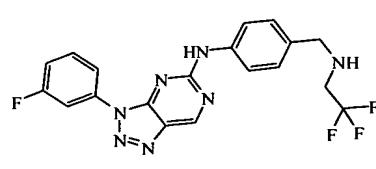
R⁸ represents C₁₋₄alkyl, polyhaloC₁₋₄alkyl or NR^{6b}R^{7b};

R^{8a} represents C₁₋₄alkyl, polyhaloC₁₋₄alkyl or NR^{6b}R^{7b}.

3. A compound as claimed in claim 1 wherein ring A represents phenyl or pyridyl; R¹ represents hydrogen; X represents a direct bond or -(CH₂)_{n3}-; R² represents phenyl or a radical of formula (b-4), wherein said R² may optionally be substituted with at least one substituent, in particular 1, 2 or 3 substituents, selected from halo; C₁₋₆alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, NR⁶R⁷, C(=O)NR⁶R⁷, C₁₋₄alkyloxy or C₁₋₄alkyloxyC₁₋₄alkyloxy; C₁₋₆alkyloxy; C₁₋₆alkyloxycarbonyl; C₁₋₄alkyloxyC₁₋₆alkyloxy; cyano; carboxyl; C(=O)NR⁶R⁷; -S(=O)_{n1}-R⁸; arylC₁₋₄alkyloxy; or a 5-or 6-membered heterocycle containing at least one heteroatom selected from O, S or N and said 5-or 6-membered heterocycle 5
10 optionally being substituted with at least one substituent selected from R⁹; R³ represents halo; hydroxy; C₁₋₆alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, NR^{6b}R^{7b} or C(=O)NR^{6b}R^{7b}; C₂₋₆alkenyl optionally substituted with at least one substituent selected from carboxyl or C₁₋₄alkyl-oxycarbonyl; polyhaloC₁₋₆alkyloxy; C₁₋₆alkyloxy optionally substituted 15
15 with C₁₋₄alkyloxy; C₁₋₆alkylthio; C₁₋₆alkyloxycarbonyl; C₁₋₆alkylcarbonyl; cyano; carboxyl; NR^{6b}R^{7b}; C(=O)NR^{6b}R^{7b}; -NR⁵-C(=O)-R⁵; -S(=O)_{n1}-R⁸; -NR⁵-S(=O)_{n1}-R⁸; or -S-CN;
R⁴ represents hydrogen; halo; C₁₋₆alkyl; cyano; hydroxy; C₁₋₆alkyloxycarbonyl; C₁₋₆alkyloxy; carboxyl; or NR⁶R⁷.
20
4. A compound as claimed in claim 1 or 3 wherein ring A represents phenyl or pyridyl; R¹ represents hydrogen; X represents a direct bond; R² represents phenyl wherein said R² may optionally be substituted with at least one substituent, in particular 1, 2 or 3 substituents, selected from halo; C₁₋₆alkyl substituted with one substituent selected 25
25 from hydroxy, cyano, NR⁶R⁷, C(=O)NR⁶R⁷, C₁₋₄alkyloxy or C₁₋₄alkyloxyC₁₋₄alkyloxy; C₁₋₆alkyloxy; C₁₋₆alkyloxycarbonyl; C₁₋₄alkyloxyC₁₋₆alkyloxy; C(=O)NR⁶R⁷; -S(=O)_{n1}-R⁸; or a 5-or 6-membered heterocycle containing at least one heteroatom selected from O, S or N and said 5-or 6-membered heterocycle optionally being substituted with at least one substituent selected from R⁹; R³ represents halo; hydroxy; C₁₋₆alkyl optionally substituted with at least one substituent selected from hydroxy, 30
30 cyano, carboxyl, C₁₋₄alkyloxy, NR^{6b}R^{7b} or C(=O)NR^{6b}R^{7b}; C₂₋₆alkenyl optionally substituted with at least one substituent selected from carboxyl or C₁₋₄alkyloxycarbonyl; polyhaloC₁₋₆alkyloxy; C₁₋₆alkyloxy optionally substituted with C₁₋₄alkyloxy or NR^{6b}R^{7b}; C₁₋₆alkylthio; C₁₋₆alkyloxycarbonyl; C₁₋₆alkylcarbonyl; 35
35 cyano; carboxyl; NR^{6b}R^{7b}; C(=O)NR^{6b}R^{7b}; -S(=O)_{n1}-R⁸; -NR⁵-C(=O)-R⁵; or -NR⁵-S(=O)_{n1}-R⁸; R⁴ represents hydrogen; halo; C₁₋₆alkyl; hydroxy; C₁₋₆alkyl-oxycarbonyl; C₁₋₆alkyloxy; carboxyl; or NR⁶R⁷.

5. A compound as claimed in any one of claims 1 to 4 wherein the R³ substituent is linked to ring A in meta position compared to the NR¹ linker.
- 5 6. A compound as claimed in any one of claims 1 to 4 wherein the R³ substituent is linked to ring A in para position compared to the NR¹ linker.
7. A compound as claimed in any one of claims 1 to 6 wherein R³ represents NR^{6b}R^{7b}.
- 10 8. A compound as claimed in any one of claims 1 to 7 wherein X represents a direct bond.
9. A compound as claimed in any one of claims 1, 5 to 8 wherein R² represents C₃₋₇cycloalkyl; phenyl; a 4, 5, 6- or 7-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N; benzoxazolyl or a radical of formula (a-1) wherein said R² substituent is substituted with at least one substituent selected from C₁₋₆alkyl substituted with NR⁶R⁷; C₂₋₆alkenyl or C₂₋₆alkynyl, each substituted with NR⁶R⁷; polyhaloC₁₋₆alkyl substituted with NR⁶R⁷; C₁₋₆alkyloxy substituted with NR⁶R⁷; polyhaloC₁₋₆alkyloxy substituted with NR⁶R⁷; or NR⁶R⁷.
- 15 20 10. A compound as claimed in any one of claims 1, 5, 6, 8 or 9 wherein R³ represents C₁₋₆alkyl substituted with NR^{6b}R^{7b}; C₂₋₆alkenyl or C₂₋₆alkynyl, each substituted with NR^{6b}R^{7b}; polyhaloC₁₋₆alkyl substituted with NR^{6b}R^{7b}; C₁₋₆alkyloxy substituted with NR^{6b}R^{7b}; polyhaloC₁₋₆alkyloxy substituted with NR^{6b}R^{7b}; or NR^{6b}R^{7b}.
- 25 11. A compound as claimed in any one of claims 1, 5, 6, 7, 8 or 10 wherein R² represents C₃₋₇cycloalkyl; phenyl; a 4, 5, 6- or 7-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N; benzoxazolyl or a radical of formula (a-1), wherein said R² substituent is substituted with at least one substituent selected from halo; polyhaloC₁₋₆alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR⁶R⁷, -C(=O)-NR⁶R⁷, -NR⁵-C(=O)-NR⁶R⁷, -S(=O)_{n1}-R⁸ or -NR⁵-S(=O)_{n1}-R⁸; polyhalo-C₁₋₆alkyloxy optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkyloxyC₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR⁶R⁷, -C(=O)-NR⁶R⁷, -NR⁵-C(=O)-NR⁶R⁷, -S(=O)_{n1}-R⁸ or -NR⁵-S(=O)_{n1}-R⁸.

12. A compound as claimed in claim 1 wherein the compound is selected from

a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine and a stereochemically isomeric form thereof.

13. A compound as claimed in any one of claims 1 to 12 for use as a medicine.

5

14. The use of a compound as defined in any one of claims 1 to 12 for the manufacture of a medicament for the prevention or the treatment of diseases mediated through GSK3.

10 15. The use of a compound as defined in any one of claims 1 to 12 for the manufacture of a medicament for the prevention or the treatment of bipolar disorder (in particular manic depression), diabetes, Alzheimer's disease, leukopenia, FTDP-17 (Fronto-temporal dementia associated with Parkinson's disease), cortico-basal degeneration, progressive supranuclear palsy, multiple system atrophy, Pick's disease, Niemann

15 Pick's disease type C, Dementia Pugilistica, dementia with tangles only, dementia with tangles and calcification, Downs syndrome, myotonic dystrophy, Parkinsonism-dementia complex of Guam, aids related dementia, Postencephalic Parkinsonism, prion diseases with tangles, subacute sclerosing panencephalitis, frontal lobe degeneration (FLD), argyrophilic grains disease, subacute sclerotizing panencephalitis (SSPE) (late complication of viral infections in the central nervous system), inflammatory diseases, depression, cancer, dermatological disorders, neuroprotection, schizophrenia, pain.

20 25 16. The use of a compound as claimed in claim 14 for the prevention or the treatment of Alzheimer's disease; diabetes; cancer; inflammatory diseases; bipolar disorder; depression; pain.

17. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredient a therapeutically effective amount of a compound as claimed in any one of claims 1 to 12.

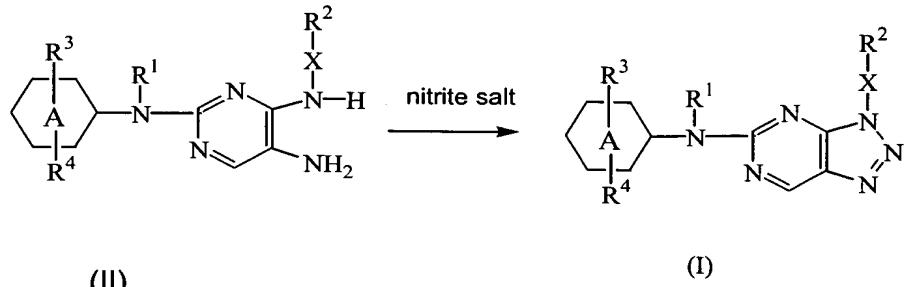
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18. A process for preparing a pharmaceutical composition as claimed in claim 17 characterized in that a therapeutically effective amount of a compound as claimed in any one of claims 1 to 12 is intimately mixed with a pharmaceutically acceptable carrier.

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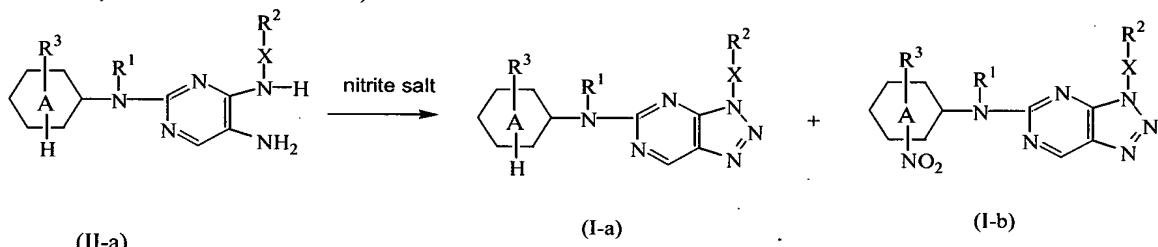
19. A process for preparing a compound as claimed in claim 1, characterized by

a) by cyclizing an intermediate of formula (II) in the presence of a nitrite salt, a suitable solvent, and a suitable acid,



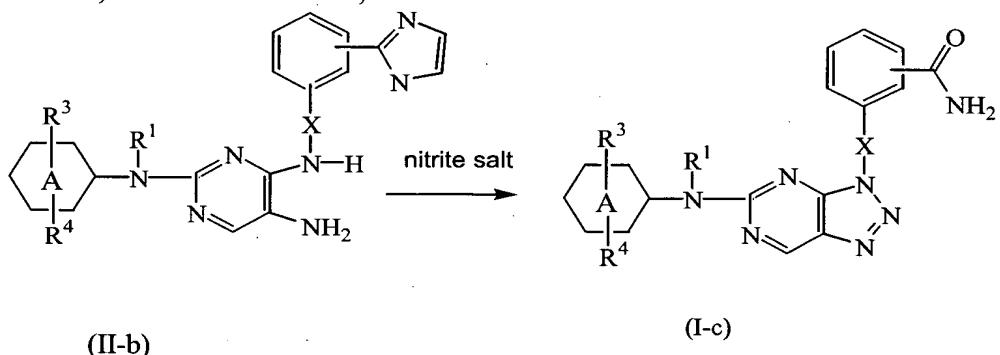
wherein ring A, R¹ to R⁴ and X are as defined in claim 1;

5 b) cyclizing an intermediate of formula (II-a) in the presence of a nitrite salt, a suitable solvent, and a suitable acid,



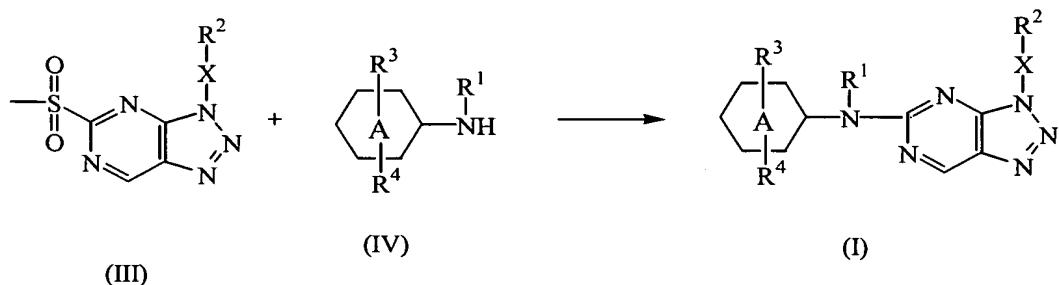
wherein ring A, R¹ to R³ and X are as defined in claim 1;

10 c) cyclizing an intermediate of formula (II-b) in the presence of a nitrite salt, a suitable solvent, and a suitable acid,



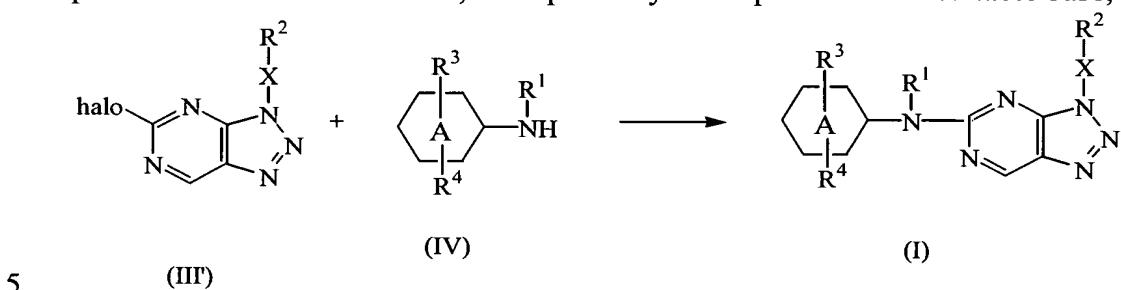
wherein ring A, R¹, R³, R⁴ and X are as defined in claim 1;

d) reacting an intermediate of formula (III) with an intermediate of formula (IV) in the presence of a suitable solvent,



wherein ring A, R¹ to R⁴ and X are as defined in claim 1;

e) reacting an intermediate of formula (III') with an intermediate of formula (IV) in the presence of a suitable solvent, and optionally in the presence of a suitable base,



5

or, if desired, converting compounds of formula (I) into each other following art-known transformations, and further, if desired, converting the compounds of formula (I), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or into a

10 therapeutically active non-toxic base addition salt by treatment with a base, or conversely, converting the acid addition salt form into the free base by treatment with alkali, or converting the base addition salt into the free acid by treatment with acid; and, if desired, preparing stereochemically isomeric forms, quaternary amines or N-oxide forms thereof.